ClinicalEvidence

Renal failure (chronic)

Search date October 2010

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ABSTRACT

INTRODUCTION: Continued progression of renal failure will lead to renal function too low to sustain healthy life. In developed countries, such people will be offered renal replacement therapy in the form of dialysis or renal transplantation. Requirement for dialysis or transplantation is termed end-stage renal disease (ESRD). METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of drug treatments used to reduce progression rate of chronic renal failure? What are the effects of lifestyle changes used to reduce progression rate of chronic renal failure? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 44 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: angiotensin II receptor antagonists, angiotensin-converting enzyme (ACE) inhibitors (with or without angiotensin II receptor antagonists), exercise, erythropoiesis-stimulating agents, fibrates, lowering blood pressure below usual targets, nicotinates, psychoeducational intervention, smoking cessation, sodium (dietary), statins, structured programmes to achieve therapeutic goals, and targeted lowering of albuminuria/proteinuria.

QUESTIONS

INTERVENTIONS

DRUGS TO REDUCE PROGRESSION

LIFESTYLE CHANGES TO REDUCE PROGRESSION

Covered elsewhere in Clinical Evidence

End-stage renal disease

To be covered in future updates

Interventions aimed at preventing cardiovascular events

Low-protein diet to reduce rate of progression to renal failure

Key points

- Chronic renal failure is characterised by a gradual and sustained decline in renal clearance or glomerular filtration rate (GFR).

  Continued progression of renal failure will lead to renal function too low to sustain healthy life. In developed countries, such people will be offered renal replacement therapy in the form of dialysis or renal transplantation. Requirement for dialysis or transplantation is termed end-stage renal disease (ESRD).

  Diabetes, glomerulonephritis, hypertension, pyelonephritis, renovascular disease, polycystic kidney disease, and certain drugs may cause chronic renal failure.

- Evidence suggests that, in people with chronic renal failure, ACE inhibitors may lower mortality and prevent or slow the progression to ESRD.

  We don't know whether angiotensin II receptor antagonists are beneficial for chronic renal failure.

  Lowering blood pressure below usual targets (with any drug) is unlikely to be beneficial.

- We don't know whether nicotinates or statins are beneficial in chronic renal disease, and the evidence shows that fibrates may have nephrotoxic effects.
- We found no evidence comparing targeted lowering of albuminuria or proteinuria versus non-targeted lowering of albuminuria or proteinuria in people with chronic renal disease.
- We don't know whether lifestyle interventions such as dietary sodium, exercise, smoking, or structured programmes to achieve therapeutic goals have an effect on chronic renal disease. However, we do know that psychoeducational interventions are likely to delay the need for renal replacement therapy.
- Evidence suggests that, in people with anaemia and chronic renal failure, erythropoiesis-stimulating agents do not lower cardiovascular events or mortality, or prevent or slow the progression to ESRD. However, erythropoiesis-stimulating agents reduce the risk of blood transfusions but increase the risk of stroke.

DEFINITION

Chronic renal failure is characterised by a gradual and sustained decline in renal clearance or glomerular filtration rate (GFR), leading to the accumulation of urea and other chemicals in the blood. There is no widely established definition. Based on limited data on healthy ageing, the Kidney Disease Improving Global Outcomes (KDIGO) statement has defined a GFR of <60 mL/minute/1.73 m^2 as indicative of chronic kidney disease. [1] This corresponds to serum creatinine concentration >137 micromol/L in men and >104 micromol/L in women. [2] KDIGO further classifies people with low GFR as follows: GFR 30 mL/minute to 60 mL/minute as stage 3; GFR 15 mL/minute to 30 mL/minute as stage 4; and GFR <15 mL/minute or a need for dialysis as stage 5 chronic kidney disease. [3] By contrast, the term chronic renal failure usually excludes people treated with dialysis or transplantation, for whom the term end-stage renal disease (ESRD) is commonly used. The term chronic renal insufficiency is also widespread in the literature, and also lacks a clear definition. [4] **For the purposes of this review, chronic renal failure, chronic renal insufficiency, and chronic kidney failure will be considered synonymous.** Chronic kidney disease, as defined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI), is a broader concept that encompasses not only low GFR but also any clinically important abnormality of kidney structure or abnormality on urine analysis (e.g., protein or blood). Progression of chronic renal failure refers to further decline in renal clearance or GFR over time. This is often assessed as an event (such as increase in serum creatinine to 50% or 100% more than previous values) or — less meaningfully from a clinical perspective — as the rate of decline of clearance (measured or estimated creatinine clearance or GFR). Continued progression of renal failure, in the absence of the competing event of death, will lead to renal function too low to sustain healthy life. In developed countries, people with this problem will usually be offered renal replacement therapy in the form of dialysis or renal transplantation. **Diagnosis:** The diagnosis of chronic renal failure is established by the finding, on at least two occasions separated by weeks or months, of elevated serum creatinine, low GFR, or low creatinine clearance. GFR and creatinine clearance may be measured directly or calculated from clinical variables and serum creatinine. [5] [6] Normal values for creatinine or GFR are the subject of some controversy. In the Framingham study of predominantly white American men and women, a subset (consisting of 3241 people who were free of known renal disease, CVD, hypertension, and diabetes) was used to define a healthy reference sample. The upper 95th percentiles for serum creatinine levels in the healthy reference sample were 136 micromol/L for men and 120 micromol/L for women. [7] In terms of GFR, on the basis of prospective longitudinal studies of healthy ageing, normal kidney function had generally been considered as a creatinine clearance of 150 mL/minute (standard deviation 20 mL/minute) for men aged 20 to 30 years, and to decline by 0.75 mL/minute a year. [8] Average clearances of 90 mL/minute to 100 mL/minute were expected in healthy older people. However, in participants in the third US National Health and Nutrition Examination Survey (NHANES III), a large proportion of the older population had low GFR (e.g., 14.5% of people in their 80s without diabetes had a GFR of 60 mL/minute/1.73 m^2 to 80 mL/minute/1.73 m^2, and a further 3.2% had a GFR of 30 mL/minute/1.73 m^2 to 60 mL/minute/1.73 m^2 [see figure 1, p 23]). [9] The distinction between decline in GFR caused by ageing and that caused by disease in older people remains controversial. KDIGO defines a GFR of <60 mL/minute/1.73 m^2 as indicative of disease. [3] Creatinine calibration varies greatly between laboratories, [10] further increasing the difficulty in setting absolute thresholds for the definition of chronic renal failure, either in terms of creatinine values, or in terms of estimates of GFR calculated from serum creatinine. [11] [12] [13] Few studies have been conducted on the cost-effective assessment of people with a new diagnosis of chronic renal failure. The rate of change of renal function, and the presence of known risk factors for chronic renal failure (e.g., diabetes, hypertension, known autoimmune or connective tissue disease, urinary tract obstruction, and family history of specific renal diseases), can be helpful diagnostically. Proteinuria and haematuria on urinalysis make glomerular or inflammatory tubulointerstitial disease more likely. [14] [15] [16] Ultrasound may be useful to exclude urinary tract obstruction. [17] [18] [19] Direct evidence about the measurement properties of clinical features or diagnostic tests in the diagnosis of unselected people with chronic renal failure is lacking, and detailed discussion of this issue is beyond the scope of this review. An opinion-based account of an approach to this problem can be found within the NKF-KDOQI guidelines. [20]

INCIDENCE/ PREVALENCE

Few data are available on the incidence of chronic renal failure. In one UK study of clinical laboratory serum creatinine values, the incidence of new chronic renal failure (defined as a single creatinine value of >180 micromol/L in men or >135 micromol/L in women [corresponding to a GFR of about 30 mL/minute/1.73 m^2]) was 0.244% a year. [21] Prevalence of a low GFR in people without diabetes is available from NHANES III, conducted in the US between 1986 and 1994 (see figure 1, p 23). [9]

AETIOLOGY/ RISK FACTORS

Little is known about the epidemiology of the underlying cause of chronic renal failure in people without diabetes in the community or in primary care. In referral centres, glomerulonephritis, hypertension or renovascular disease, and polycystic kidney disease are the most common diagnoses, with a smaller proportion of people having tubulointerstitial disease or vasculitis. [22] [23] [24] In people with chronic renal failure who progress to ESRD in Canada, diabetes is the most common cause (24%), followed by glomerulonephritis (20%), unknown (14%), hypertension (10%), pyelonephritis (7%), renovascular disease (7%), polycystic kidney disease (6%), and drug-induced disease (commonly by lithium, analgesics, and NSAIDs, 2%). [25]

PROGNOSIS

A 10-year, community-based cohort study in Japan found that higher serum creatinine levels may lead to an increase in the risk of developing ESRD. [26] In a community-based cohort in Tromsø, Norway, the 10-year cumulative incidence of renal failure (identified through clinical laboratory screening as having a GFR of 30–60 mL/minute/1.73 m^2) was 4% (95% CI 3% to 6%) and mortality was 51% (95% CI 48% to 55%). [27] In a 5-year follow-up of a cohort identified through the laboratories of a large managed care organisation in the US, the rate of ESRD was 1% and mortality 24% for people with a GFR of 30 mL/minute/1.73 m^2 to 60 mL/minute/1.73 m^2, and ESRD was 20% and mortality 46% for those with a GFR of 15 mL/minute/1.73 m^2 to 30 mL/minute/1.73 m^2. [28] In a cohort study of men with serum creatinine >300 micromol/L and women with serum creatinine >250 micromol/L, identified through clinical laboratories, 80% reached ESRD at follow-up of 55 to 79 months. [29] In a UK community-based study of clinical laboratory serum creatinine values, chronic renal failure was defined as a single creatinine value of >180 micromol/L in men or >135 micromol/L in women (corresponding to a GFR of about 30 mL/minute/1.73 m^2). [21] In those people meeting this definition, but who had not been referred to a nephrologist, and in whom repeat serum creatinine levels were obtained, the annual rate of decline in GFR was <2 mL/minute/year in 79% of people and 5 mL/minute/year or greater in 8% of people. In the NHANES III (conducted between 1986 and 1994), 4.3% of the group had a low GFR (30–60 mL/minute/1.73 m^2) and 0.2% had a very low GFR (15–30 mL/minute/1.73 m^2). [1] In addition, in the United States Renal Data Survey (USRDS) for 1990, 0.06% of the group required renal replacement therapy. [30] The data from these two studies strongly suggest that many unreferred people with a low GFR do not have progressive disease, or are either of an age or carrying a burden of comorbidity, such that the competing risk of death outweighs the risk of ESRD. Proteinuria is a consistent multivariable risk factor for progression of renal failure and for ESRD [23] [31] [32] and can be classified in many ways. Frequently used classification systems are: dipstick (0, 1+, 2+, and 3+); albuminuria (sometimes divided into microalbuminuria and macroalbuminuria depending on the degree of albumin excretion, the collection method, and units used); and proteinuria (non-proteinuric [<300 mg/day], non-nephrotic range proteinuria [300–3000 mg/day], and nephrotic range proteinuria [>3000 mg/day]). Hypertension and cigarette smoking have also been shown to be risk factors for progression to ESRD. [33] People referred to nephrologists differ from those in primary care in both prognostic markers and rates of progression. For example, in the Modification of Diet in Renal Disease (MDRD) study A (GFR 25–55 mL/minute/1.73 m^2), 27% of participating people had >1000 mg daily proteinuria, [33] whereas in NHANES III only 3% of participants with a GFR of 30 mL/minute/1.73 m^2 to 60 mL/minute/1.73 m^2 showed >288 mg daily of albuminuria. [34] Rate of progression also seems to differ between referred and unreferred people. In a review summarising studies of mostly referred people, the weighted mean loss of GFR was 7.56 mL/minute/year. [35] By contrast with this, in a community-based study of unreferred people conducted in the UK, only 21% of people showed evidence of progression of renal disease (defined as at least 2.0 mL/minute/1.73 m^2 a year), and the remaining 79% showed no evidence of progression (see table 1, p 24). [21]

AIMS OF INTERVENTION

To prevent ESRD or prolong time before renal replacement therapy is required; to prevent death; to prevent progression of renal disease to levels of kidney function at which cardiovascular morbidity and mortality increases substantially and at which metabolic complications (malnutrition, hyperparathyroid bone disease, and anaemia) occur, with minimal adverse effects of treatment.

OUTCOMES

Short-term outcomes: adverse effects of treatment, including hyperkalaemia, hypokalaemia, elevated creatinine kinase. **Long-term outcomes: mortality** (all cause; mortality caused by MI, congestive heart failure, or stroke); **cardiovascular effects:** morbidity (caused by MI, congestive heart failure, or stroke); **renal disease progression**; time to requirement of renal replacement

therapy/initiation of dialysis; progression of renal disease (usually defined by the outcome cluster initiation of dialysis or increase in creatinine by some fixed amount or percentage change from baseline). Where rate of decline of GFR was the primary outcome of the study, these data were extracted in addition to data on time to requirement of renal replacement therapy or progression of renal disease (because such studies were likely to be underpowered to show a difference in these clinically important outcomes); **quality of life**; **adverse effects of treatment**.

METHODS

Clinical Evidence search and appraisal October 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to October 2010, Embase 1980 to October 2010, and The Cochrane Database of Systematic Reviews, October 2010 (online; 1966 to date of issue). When editing this review we used The Cochrane Database of Systematic Reviews 2010, Issue 4. An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, including open studies, and containing more than 20 individuals who were followed up for a minimum of 6 months. We didn't specify a maximum loss to follow-up for inclusion. For the option on erythropoiesis-stimulating agents, we required a trial size of at least 50 patients per arm. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 25). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of drug treatments used to reduce progression rate of chronic renal failure?**

OPTION **ACE INHIBITORS**

Disease progression

Compared with control ACE inhibitors may be more effective at reducing the risk of disease progression and of end-stage renal disease (ESRD) in people with chronic renal failure (low-quality evidence).

Mortality

Compared with control ACE inhibitors may be more effective at reducing mortality in people with chronic renal failure (very low-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits:

ACE inhibitors versus placebo or no treatment:

We found one systematic review [36] and two subsequent RCTs. [22] [37]

The systematic review (search date 1997) identified 11 RCTs of 1860 people (mean glomerular filtration rate [GFR] not reported; mean serum creatinine 203 micromol/L, standard deviation [SD] 106 micromol/L; mean proteinuria 1.8 g/day, SD 2.3 g/day). [36] People were randomised to ACE inhibitor versus placebo in 5 RCTs, ACE inhibitor versus atenolol or acebutolol in three RCTs, ACE inhibitor versus nifedipine in two RCTs, and ACE inhibitor versus comparator (not specified) in one RCT. Angiotensin II receptor antagonists were not permitted in either group in any study. In all studies, additional antihypertensive drugs were used in both groups to control blood pressure to targets <140/90 mmHg. Fewer people reached end-stage renal disease (ESRD) or died with ACE inhibitors than with controls; however, the difference in mortality was not significant (ESRD: 70/941 [7%] with ACE inhibitors *v* 106/919 [12%] with controls; RR 0.69, 95% CI 0.51 to 0.94; doubling of serum creatinine or ESRD: 124/941 [13%] with ACE inhibitors *v* 187/919 [20%] with controls; RR 0.70, 95% CI 0.55 to 0.88; death: 20/941 [2%] with ACE inhibitors *v* 11/919 [1%] with controls; RR not reported; P = 0.12).

The first subsequent RCT (224 people with serum creatinine 274–442 micromol/L and >0.3 g/day proteinuria for at least 3 months; mean GFR 26.3 mL/minute/1.73 m^2, SD 5.3 mL/minute/1.73 m^2; mean serum creatinine 354 micromol/L, SD 62 micromol/L; mean proteinuria 1.6 g/day, SD 0.7 g/day) found that benazepril 20 mg daily significantly reduced the composite outcome of doubling of serum creatinine, ESRD, or death compared with placebo over 3.4 years (44/107 [41%] with benazepril *v* 65/108 [60%] with placebo; RR not reported; P = 0.004; analysis was not by intention to treat). [22] This trial was not confounded by blood-pressure-lowering effects: open-label drugs other than ACE inhibitors and angiotensin II receptor antagonists were added as needed to maintain the same target blood pressure (systolic blood pressure <130 mmHg, diastolic blood pressure <80 mmHg) in both arms. The decline in blood pressure was similar in the two groups (absolute numbers presented graphically; P = 0.18).

The second subsequent RCT (8280 people, all at least 50 years old with stable coronary artery disease and normal or mildly reduced left ventricular function [ejection fraction >40%] and serum creatinine <177 micromol/L) was a subgroup analysis of the Prevention of Events with ACE inhibition trial (PEACE). It compared trandolapril (target, 4 mg/day) versus placebo with a median follow-up of 4.8 years. [37] The RCT found that trandolapril significantly reduced all-cause mortality compared with placebo (adjusted HR 0.73, 95% CI 0.54 to 1.00; P = 0.05) in people with a GFR of <60 mL/minute/1.73 m^2. Similar trends were found for cardiovascular mortality, but not for the composite outcome of cardiovascular death or non-fatal MI, or for the primary composite outcome of cardiovascular death, non-fatal MI, or revascularisation. No comparative data were reported for outcomes other than all-cause mortality. [37]

ACE inhibitors versus angiotensin II receptor antagonists:
See benefits of angiotensin II receptor antagonists, p 7 .

Harms:

ACE inhibitors versus placebo or no treatment:
The review reported more withdrawals with ACE inhibitors compared with controls (withdrawals: 40/941 [4%] with ACE inhibitors *v* 15/919 [2%] with controls; P = 0.001; withdrawals owing to non-fatal CVD: 18/941 [2%] with ACE inhibitors *v* 18/919 [2%] with controls; P >0.2; withdrawals owing to other non-fatal event: 55/941 [6%] with ACE inhibitors *v* 35/919 [4%] with controls; P = 0.04). [36] In the first subsequent RCT, 57/281 (20%) people were excluded while taking benazepril 10 mg daily during an active drug run-in period (dry cough: 42/281 [15%]; >30% increase in serum creatinine: 6/281 [2%]; hyperkalaemia: 4/281 [1%]). During the study, 11/224 (5%) people developed hyperkalaemia, of whom 8 were successfully treated medically and three withdrew (distribution of people between groups not reported). [22] Serum potassium levels were significantly higher among people receiving benazepril compared with placebo (P = 0.001), although the difference never exceeded 0.5 mmol/L (absolute numbers not reported). The proportion of people receiving erythropoietin, mean dose of erythropoietin, and haemoglobin levels were similar between groups (effect size and significance level not reported). The second subsequent RCT gave no information on adverse effects. [37]

ACE inhibitors versus angiotensin II receptor antagonists:
See harms of angiotensin II receptor antagonists, p 7 .

Comment:

In people at high risk of ESRD (women with serum creatinine >146 micromol/L; men with serum creatinine >177 micromol/L; people with GFR or creatinine clearance <30 mL/minute/1.73 m^2; people in whom proteinuria coexists with abnormal renal function or known renal disease; and people in whom renal disease is progressing [serum creatinine rising or GFR falling]), ACE inhibitors are likely to reduce the risk of progression of disease and ESRD. In other people, the risk of ESRD is lower, and the risk of CVD dominates the clinical picture. In these people, the overall cardiovascular risk profile should be taken into account in deciding which preventive treatments are most likely to be beneficial.

OPTION ACE INHIBITORS PLUS ANGIOTENSIN II RECEPTOR ANTAGONISTS VERSUS EITHER DRUG ALONE

Disease progression
Compared with ACE inhibitors or with angiotensin II receptor antagonists alone ACE inhibitors plus angiotensin II receptor antagonists may be more effective at reducing disease progression or end-stage renal disease (ESRD) in people with chronic renal failure at 3 years (very low-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits:

ACE inhibitors plus angiotensin II receptor antagonists versus ACE inhibitors or angiotensin II receptor antagonists alone:
We found no systematic review, but found 4 RCTs. [38] [39] [40] [41]

The first RCT comparing angiotensin II receptor antagonist versus ACE inhibitor in the COOPERATE non-diabetic renal disease trial [38] was criticised for statistical and methodological implausibilities [42] and has been withdrawn. [43] No rebuttal from the authors of the original trial has appeared. We therefore excluded this study from our review.

The second RCT compared perindopril 4 mg daily plus candesartan 8 mg daily (25 people) versus perindopril 4 mg daily (25 people) in people with chronic renal failure (glomerular filtration rate [GFR] 25–35 mL/minute; serum creatinine not reported; proteinuria 2.5–6.5 g/day; all treated with low-protein diet [0.6 g/kg/day] and ketoacids [100 mg/kg/day]). [39] At 1-year follow-up, perindopril plus candesartan significantly reduced the rate of GFR decline (reduction of GFR by inulin clearance over 1 year: 0.66 mL/minute/1.73 m^2 with perindopril plus candesartan *v* 1.5 mL/minute/1.73 m^2 with perindopril alone; P <0.01). The proportion of people with progression of renal disease or end-stage renal disease (ESRD) was not reported.

The third RCT compared three interventions: losartan 25 mg daily plus enalapril 10 mg daily (16 people), losartan 25 mg daily (18 people), and enalapril 10 mg daily (18 people). [40] Creatinine clearance and serum creatinine did not differ between groups during the 9-month observation period (absolute results presented graphically; significance not reported).

The fourth RCT (90 Japanese people with hypertension and serum creatinine concentration 106–442 micromol/L; mean age 60 years; 40% male; 51–53% with IgA nephropathy, 18% with glomerulonephritis, 7% with membranous nephropathy, and 22–24% with unknown renal disease; mean serum creatinine about 265 micromol/L; mean creatinine clearance about 38 mL/minute; mean proteinuria 1.6–1.7 g/day) compared ACE inhibitor plus candesartan (2–12 mg/day) versus ACE inhibitor alone with a 3-year follow-up. [41] The RCT did not describe how the dose of ACE inhibitor or angiotensin II receptor blocker was determined. The average final doses given were: 4.5 mg daily in people taking benazepril plus candesartan 8 mg; 4.2 mg daily in people randomised to no candesartan; 2.4 mg daily for people taking trandolapril plus candesartan 8 mg; and 2.8 mg daily for people randomised to no candesartan. Final dose of candesartan was 8.5 mg daily; 80% of people assigned to candesartan took 8 mg daily. Blood pressure targets were <130/80 mmHg for both groups. The RCT found that the achieved blood pressure was similar in both groups (129/78 mmHg with ACE inhibitor plus candesartan *v* 130/80 mmHg with ACE inhibitor alone; P value not reported; 82% of people assigned to ACE inhibitor plus candesartan and 80% of people assigned to ACE inhibitor alone achieved the target of <130/80 mmHg). Doubling of serum creatinine occurred in 0/45 (0%) of people with ACE inhibitor plus candesartan versus 7/45 (16%) of people with ACE inhibitor alone; 2/45 (4%) in each group reached ESRD (no significance assessment performed). The RCT found that both groups achieved similar blood pressure targets (129/78 mmHg with ACE inhibitor plus candesartan *v* 130/80 mmHg with ACE inhibitor alone; P value not reported). [41]

Harms:

The first RCT was excluded. [38] The second and third RCTs did not assess harms. [39] [40] The fourth RCT reported that both candesartan and ACE inhibitors were well tolerated; no further information given. [41]

We identified one systematic review of harms that did not examine efficacy issues. [44] This systematic review included data from the excluded COOPERATE study [38] (discredited, see benefits) and from 4 other RCTs of 107 people in total. In these 4 RCTs, there were no withdrawals because of acute kidney injury or hyperkalaemia. In one of these RCTs, potassium above 6.0 mmol/L occurred in 2/16 (13%) people on ACE inhibitor plus angiotensin II receptor antagonist. [44]

Comment:

Most data derive from the second [39] and fourth [41] RCTs in which mean proteinuria was above 1 g daily. It is uncertain whether the benefits of combination treatment extend to people with a lower degree or no proteinuria. Furthermore, the dose of perindopril (4 mg) in the second RCT is half the recommended upper limit for the treatment of hypertension, and the dose of ACE inhibitors at baseline in the fourth RCT was not specified by the protocol or reported in the results, and it may not have been maximal. It is unclear whether the benefits observed in these studies might also have been achieved with a maximal dose of ACE inhibitor alone.

The renal subgroup analyses from the ONTARGET study, published after our search date, show no benefit from combined treatment in any subgroup, including those with GFR less than 30 mL/minute/1.73 m^2 and macroalbuminuria. [45] People in this large study were selected on the basis of vascular disease and few had more than 1 g of protein. [45] It is for people with this level or greater of proteinuria that evidence is still very limited and conflicting.

OPTION FIBRATES

Disease progression

Compared with placebo Gemfibrozil, a fibrate, may increase the progression of renal disease in people with chronic renal failure compared with placebo (low-quality evidence).

Note
Fibrates are unlikely to have a beneficial effect on preservation of kidney function, and may even be harmful.

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits: We found no systematic review. We found one RCT (subgroup analysis of a larger RCT of 2531 men) comparing gemfibrozil with placebo (1046 men; creatinine clearance <75 mL/minute; mean age 67 years, standard deviation [SD] 5 years; 27–30% with diabetes; mean glomerular filtration rate (GFR) 61.6 mL/minute/1.73 m^2, SD 12.0 mL/minute/1.73 m^2; mean serum creatinine and proteinuria not reported). At mean follow-up of 5.3 years, men treated with gemfibrozil had a significantly greater progression of renal disease compared with men treated with placebo (44.2 micromol/L increase in serum creatinine: 6% men with gemfibrozil *v* 3% men with placebo; absolute numbers not reported; P = 0.02). End-stage renal disease (ESRD) did not occur in either group. [46]

Harms: The RCT found no significant difference in adverse effects (serum creatine phosphokinase levels >3 times the upper limit of normal, abnormalities in liver function tests, or rhabdomyolysis) between gemfibrozil and placebo (P >0.05). [46]

Comment: In 6% to 40% of people, fibrates seem to cause sustained increases in serum creatinine, which occur 1 week to 5 months after initiation of fibrate, and which are often reversible on discontinuation. [46] [47] However, baseline chronic renal failure has not been shown to be a risk factor for this complication. Renal adverse effects would not be commonly expected with statins, and RCTs have shown that muscle and liver toxicity is low in people with chronic renal failure or ESRD treated with either simvastatin, or the combination of simvastatin and ezetimibe. [48] [49]

Clinical guide:
The large RCT suggests that fibrates are unlikely to have a beneficial effect on preservation of kidney function, and may even be harmful. [46] Their use in people with chronic renal failure who also have cardiovascular risk factors will depend on an assessment of the trade-off between the benefits of the treatment from a cardiovascular perspective, and the possibility of harm from a renal perspective. It should also take into account what other options (see statins, p 9) are available for the management of the cardiovascular risk profile.

OPTION ANGIOTENSIN II RECEPTOR ANTAGONISTS

Disease progression
Compared with placebo Angiotensin II receptor antagonists may be more effective at reducing glomerular filtration rate (GFR) in people with chronic renal failure (low-quality evidence).

Compared with ACE inhibitors We don't know whether angiotensin II receptor antagonists are more effective at preventing disease progression or end-stage renal disease (ESRD) in people with chronic renal failure (very low-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits: **Angiotensin II receptor antagonists versus placebo:**
We found two RCTs, the first of which compared valsartan versus placebo for 6 months (56 people; mean age: 54 years with valsartan *v* 56 years with placebo; proportion of men: 57% with valsartan *v* 62% with placebo; mean glomerular filtration rate (GFR) 19.5 mL/minute/1.73 m^2 with valsartan *v* 22.0 mL/minute/1.73 m^2 with placebo; proteinuria and albuminuria not reported). [50] The reduction in GFR (measured by ^{51}Cr ethylenediaminetetra-acetic acid [EDTA]) was similar in both groups (GFR reduction from 19.2 mL/minute/1.73 m^2 to 17.6 mL/minute/1.73 m^2 [geometric mean; arithmetic mean and standard deviation not reported] with valsartan *v* from 21.2 mL/minute/1.73 m^2 to 16.5 mL/minute/1.73 m^2 with placebo; P = 0.577). Analysis was not by intention to treat. This study was not confounded by ACE inhibitor use, as ACE inhibitors were prohibited in both groups. Systolic and diastolic blood pressure differed between the two groups (absolute results shown graphically; P <0.001 for systolic blood pressure; P <0.002 for diastolic blood pressure).

The second RCT (109 Chinese people with IgA nephropathy; mean age 40–41 years; 38% male; mean serum creatinine 98–114 mmol/L; mean GFR 78–87 mL/minute/1.73 m^2; mean proteinuria 1.8–2.3 g/day) compared valsartan (80–160 mg/day) versus placebo for 2 years. [51] The primary end point for the RCT was the composite outcome of time to doubling of the baseline serum creatinine level or the development of end-stage renal disease (ESRD) that required renal replacement

therapy; the secondary outcome measures were decrease in proteinuria and rate of GFR decrease. [51] Target blood pressure was 140/90 mmHg for both groups. The RCT found no significant difference between groups in the composite outcome of progression to ESRD or doubling in serum creatinine level (1/54 [2%] with valsartan *v* 4/55 [7%] with placebo; P = 0.18; further data not reported) at 2 years. The RCT found that, compared with placebo, valsartan significantly decreased proteinuria (P = 0.001) and slowed the mean rate of decline of GFR at 2 years (P = 0.025; absolute data for both outcomes presented graphically). [51]

Angiotensin II receptor antagonists versus ACE inhibitors:
We found no systematic review. We found two RCTs comparing angiotensin II receptor antagonists versus ACE inhibitors.

The first RCT (68 people with non-diabetic kidney disease and a GFR of 25–59 mL/minute; mean age 50 years; 57% male; serum creatinine 203–251 micromol/L; mean GFR 38–44 mL/minute/1.73 m^2; mean proteinuria 2.1–2.6 g/day) compared an angiotensin II receptor antagonist (candesartan 2–8 mg/day or losartan 25–100 mg/day) versus an ACE inhibitor (benazepril 1.25–5 mg/day or trandolapril 0.5–4 mg/day) for 5 years. [52] The primary end point for this RCT was change in GFR; secondary end points included serum creatinine level, urinary protein excretion, and blood pressure, as well as the rate of development of ESRD. The RCT found no significant difference in GFR at 5 years (reported as not significant; absolute data presented graphically; P value not reported); this analysis did not include any data for people who had begun dialysis treatment. By year 5, ESRD developed in 19/36 (53%) people on ACE inhibitors and 26/32 (81%) people on angiotensin II receptor antagonists (RR not reported; P <0.01). Doubling of creatinine or ESRD was not reported. The RCT found no significant difference in GFR at 5 years (reported as not significant; absolute data presented graphically; P value not reported); this analysis did not include any data on people who had begun dialysis treatment. During years 1 to 4, creatinine was lower and the estimated creatinine clearance was higher in people taking ACE inhibitors than in people taking angiotensin II receptor antagonists (also excluding people who developed ESRD). There was no significant difference in blood pressure (reported as not significant; absolute data presented graphically; P value not reported); both groups achieved the target blood pressure of 130/80 mm/Hg. However, the RCT reported no significant difference between angiotensin II receptor antagonists and ACE inhibitors in the rate of progression to ESRD (26/32 [81%] with angiotensin II receptor inhibitors *v* 19/36 [53%] with ACE inhibitors; P = 0.004; no further data reported). There were no deaths or cardiovascular events reported. [52]

The second RCT (306 people with creatinine 133–442 micromol/L; creatinine clearance 20–70 mL/minute/1.73 m^2; non-diabetic kidney disease and at least 1 g/day proteinuria for at least 3 months; age 49–51 years; mean creatinine 239–256 micromol/L; mean GFR 30–31 mL/minute/1.73 m^2; proportion with diabetes not specified; mean 24-hour urine protein excretion 1.4–2.1 g/day) compared 4 groups: low-dose benazepril 10 mg daily; losartan 50 mg daily; individualised up-titrated benazepril 40 mg daily; or individualised up-titrated losartan 200 mg daily, based on 24-hour urine protein with a mean follow-up of 3.7 years. [53] The primary end point for this RCT was time to the composite of a doubling of the serum creatinine, ESRD, or mortality. For a full description of the titration protocol please see Targeted versus non-targeted lowering of albuminuria/proteinuria, p 11 . The RCT found no significant difference between benazepril and losartan for the composite primary end point of doubling of serum creatinine, ESRD, or mortality among people treated with up-titrated drug (15/84 [18%] with up-titrated benazepril *v* 13/84 [16%] with up-titrated losartan; reported as not significant; P value not reported). The RCT found no significant difference between benazepril and losartan for the composite primary end point of doubling of serum creatinine, ESRD, or mortality among people treated with non-titrated drug (26/83 [31%] with non-titrated benazepril *v* 26/88 [30%] with non-titrated losartan; reported as not significant; P value not reported). [53] The RCT reported similar rates of non-fatal cardiovascular events, MI, heart failure, and stroke in each group (up-titrated benazepril: 5/90 [6%] with non-fatal CVD event, 2/90 [2%] with MI, 1/90 [1%] with heart failure, 1/90 [1%] with stroke; up-titrated losartan: 4/90 [4%] with non-fatal CVD event, 2/90 [2%] with MI, 1/90 [1%] with heart failure, 1/90 [1%] with stroke; non-titrated benazepril: 4/90 [4%] with non-fatal CVD event, 2/90 [2%] with MI, 1/90 [1%] with heart failure, 1/90 [1%] with stroke; non-titrated losartan: 5/90 [6%] with non-fatal CVD event, 2/90 [2%] with MI, 2/90 [2%] with heart failure, 1/90 [1%] with stroke). No significance assessments between groups were reported.

Harms:

Angiotensin II receptor antagonists versus placebo:
The first RCT reported premature discontinuation of drug for increasing serum creatinine, dizziness, and nausea (increasing serum creatinine: 3/30 [10%] with valsartan *v* 2/26 [8%] with placebo; creatinine elevation persisted in all cases after discontinuation of drug; dizziness: 1/30 [3%] with valsartan *v* 0/26 [0%] with placebo; nausea: 0/30 [0%] with valsartan *v* 1/26 [4%] with placebo). [50] Adverse effects included dizziness, increase in serum creatinine, hypotension, hyperkalaemia, syncope, and total events (dizziness: 4/30 [13%] with valsartan *v* 2/26 [8%] with placebo; increase

in serum creatinine: 3/30 [10%] with valsartan *v* 3/26 [12%] with placebo; hypotension: 3/30 [10%] with valsartan *v* 1/26 [4%] with placebo; hyperkalaemia: 2/30 [7%] with valsartan *v* 0/26 [0%] with placebo; syncope: 2/30 [7%] with valsartan *v* 0/26 [0%] with placebo; total events: 14/30 [47%] with valsartan *v* 6/26 [23%] with placebo; significance not reported). The second RCT reported allergy or angio-oedema, heart failure, withdrawal, dizziness, headache, palpitations, and ankle oedema (allergy or angio-oedema: 0/54 [0%] with valsartan *v* 1/55 [2%] with placebo; heart failure: 0/54 [0%] with valsartan *v* 1/55 [2%] with placebo; withdrawal: 0/54 [0%] with valsartan *v* 1/55 [2%] with placebo; dizziness: 1/54 [2%] with valsartan *v* 2/55 [4%] with placebo; headache: 1/54 [2%] with valsartan *v* 2/55 [4%] with placebo; palpitations: 2/54 [4%] with valsartan *v* 3/55 [6%] with placebo; ankle oedema: 1/54 [2%] with valsartan *v* 2/55 [4%] with placebo; no significance assessments performed for any comparison). [51]

Angiotensin II receptor antagonists versus ACE inhibitors:
The first RCT reported that 1/32 (3%) people stopped losartan for reasons not specified and 2/36 (6%) people stopped ACE inhibitors owing to dry cough. There were no serious drug-related adverse events during the 5 years of the study. [52] The second RCT reported that hyperkalaemia occurred in 5/90 (6%) people with up-titrated benazepril, 5/90 (5%) people with up-titrated losartan, 3/90 (3%) people with non-titrated benazepril, and 3/90 (3%) people with non-titrated losartan; acute decline in renal function occurred in 3/90 (3%) people with up-titrated benazepril, 3/90 (3%) people with up-titrated losartan, 2/90 (2%) people with non-titrated benazepril, and 3/90 (3%) people with non-titrated losartan; dry cough in 15/90 (17%) people with up-titrated benazepril, 0/90 (0%) people with up-titrated losartan, 17/90 (19%) people with non-titrated benazepril, and 0/90 (0%) people with non-titrated losartan; and hypotension in 2/90 (2%) people with up-titrated benazepril, 1/90 (1%) people with up-titrated losartan, 1/90 (1%) people with non-titrated benazepril, and 1/90 (1%) people with non-titrated losartan (no direct comparisons made between groups).

Comment: In people at high risk of ESRD (women with serum creatinine >146 micromol/L; men with serum creatinine >177 micromol/L; people with GFR or creatinine clearance <30 mL/minute/1.73 m^2; people in whom proteinuria coexists with abnormal renal function or known renal disease; and people in whom renal disease is progressing [serum creatinine rising or GFR falling]), evidence from systematic reviews (specifically of ACE inhibition; see benefits of ACE inhibitors, p 4) suggests that ACE inhibition is likely to reduce the risk of progression of disease and ESRD. However, there is no evidence that angiotensin II receptor antagonists prevent progression of disease and ESRD. Because both ACE inhibitors and angiotensin II receptor antagonists act on the renin-angiotensin system, it is reasonable to use angiotensin II antagonists in people unable to tolerate ACE inhibitors because of cough. However, incidence of other adverse effects — such as increase in serum creatinine and hyperkalaemia — is likely to be similar with both drugs. In people at lower risk of ESRD, the risk of CVD dominates the clinical picture. In these people, the overall cardiovascular risk profile should be taken into account when deciding which preventive therapies are most likely to be beneficial.

OPTION NICOTINATES

Disease progression
Compared with no nicotinates We don't know whether nicotinates are more effective at reducing disease progression or end-stage renal disease (ESRD) in people with chronic renal failure (moderate-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits: We found no systematic review. We found one RCT comparing (33 people, mean age 54–61 years, mean creatinine clearance 46 mL/minute, standard deviation [SD] 31 mL/minute; mean serum creatinine 177 micromol/L, SD 132.6 micromol/L; mean proteinuria 3.17 g/day, SD 2.66 g/day; mean total cholesterol 5.53 mmol/L, SD 1.6 mmol/L) comparing niceritrol versus no niceritrol. [54] End-stage renal disease (ESRD) and progression of renal disease were not reported. At 1-year follow-up, there was no significant difference in reduction in creatinine clearance with niceritrol compared with control (creatinine clearance change –1 mL/minute, SD 13 mL/minute, with niceritrol *v* –10 mL/minute, SD 12 mL/minute, with control; P = 0.06).

Harms: The RCT reported facial flushing in 1/16 (6%) people taking niceritrol. [54]

Comment: None.

OPTION STATINS

Disease progression

Compared with placebo or no treatment We don't know whether statins are more effective than controls at reducing disease progression or end-stage renal disease (ESRD) in people with chronic renal failure (low-quality evidence).

Mortality
Compared with placebo or no treatment Statins seem to be more effective at reducing mortality in people with chronic renal failure (moderate-quality evidence)

Cardiovascular effects
Compared with placebo or no treatment Statins may be more effective at reducing major coronary events (low-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits:

Statins versus placebo or no treatment (not using statins):
We found three systematic reviews [55] [56] [57] and 4 subsequent RCTs. [58] [59] [60] [61]

The first systematic review (search date 2005) identified 27 RCTs of nearly 40,000 people (aged 32–65 years, median age 55 years; sex distribution not reported; glomerular filtration rate [GFR] range 41–91 mL/minute, median 77 mL/minute; proteinuria range 0.01–6.70 g/day, median 0.84 g/day). [55] The proportion of people with progression of renal disease or end-stage renal disease (ESRD) was not reported. People in the statins group had a lower GFR reduction compared with control (WMD of GFR reduction 1.22 mL/minute/year with statins *v* controls, 95% CI 0.44 mL/minute/year to 2.00 mL/minute/year; P = 0.002). However, there was substantial heterogeneity (I^2 = 96.3%) between the original studies included in the meta-analysis.

The second systematic review (search date 2006, 26 RCTs, 16 of which were identified by the first review; 25,017 people with chronic kidney disease; median GFR 56 mL/minute/1.73 m^2; median cholesterol 6.63 mmol/L; proteinuria not reported) compared statins versus placebo. [56] The systematic review found that, compared with placebo or no treatment, statins significantly reduced all-cause mortality (5 RCTs; 708/9049 [8%] with statin *v* 883/9127 [10%] with placebo or no treatment; RR 0.81, 95% CI 0.74 to 0.89; P <0.001) and cardiovascular mortality over 3 to 60 months (4 RCTs; 1391/9622 [15%] with statins *v* 1806/9741 [19%] with placebo or no treatment; RR 0.75, 95% CI 0.66 to 0.85; P <0.001). [56] Creatinine clearance (either in mL/minute or mL/minute/1.73 m^2) did not change with statins by comparison with placebo (11 RCTs, 548 people; WMD +1.48 mL/minute, 95% CI −2.32 mL/minute to +5.28 mL/minute). [56]

The third systematic review [57] is a Cochrane review, reporting the same meta-analysis of 26 RCTs, by the same authors, as the second systematic review above. [56]

The first subsequent RCT (2314 people with GFR <75 mL/minute/1.73 m^2; mean age 61 years; 74% men; 4–5% with diabetes; mean total cholesterol 6.8 mmol/L; mean serum creatinine 101 micromol/L; mean GFR 65 mL/minute; proteinuria not reported) compared simvastatin (20–40 mg/day, titrated to decrease total cholesterol levels to <5.2 mmol/L) versus placebo with a median follow-up of 5.4 years. [58] It found that simvastatin significantly decreased the risk of all-cause mortality, major coronary events, and a composite outcome of death from coronary disease and non-fatal MI compared with placebo (all-cause mortality: HR 0.70, 95% CI 0.55 to 0.91; major coronary events: HR 0.68, 95% CI 0.57 to 0.80; composite outcome of death from coronary disease and non-fatal MI: HR 0.66, 95% CI 0.55 to 0.79; absolute numbers not reported). However, it found no difference in stroke (HR 0.86, 95% CI 0.54 to 1.36; absolute numbers not reported). [58]

The second subsequent RCT (10,060 people with hypertension and one other coronary risk factor; mean age 67 years; 51% male; 58–59% with GFR 60–89 mL/minute/1.73 m^2, 16% with GFR <60 mL/minute/1.73 m^2, mean GFR 79 mL/minute/1.73 m^2; mean cholesterol 5.8 mmol/L; proteinuria not measured) compared pravastatin 40 mg daily versus usual care (undefined) over 6 years. [59] This paper reported a post-hoc analysis of kidney disease outcomes in participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). The RCT found no significant difference between pravastatin and usual care in progression to ESRD (56/5170 [1%] with pravastatin *v* 58/5185 [1%] with usual care; P = 0.9), composite outcome of ESRD or 50% decrease in GFR (159/4535 [4%] with pravastatin *v* 157/4461 [4%] with usual care; P = 0.9), or the composite outcome of ESRD or 25% decrease in GFR (881/4535 [19%] with pravastatin *v* 992/4461 [20%] with usual care; P = 0.3; no further data reported). There was no significant difference in the risk of ESRD between groups in a subgroup analysis with GFR <45 mL/minute/1.73 m^2 (323 people; HR 0.77, 95% CI 0.41 to 1.45; P value and absolute numbers not reported). [59]

The third subsequent RCT, a subgroup analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS; 304 men and postmenopausal women aged 45–73 years with GFR <60 mL/minute/1.73 m^2; mean age 62 years; 77% men; 2% with diabetes; mean total

cholesterol 5.7 mmol/L, standard deviation [SD] 0.62 mmol/L; mean serum creatinine 124 micromol/L, SD 18 micromol/L; mean GFR 53 mL/minute/1.73 m^2, SD 6 mL/minute/1.73 m^2; mean proteinuria not reported) compared lovastatin 20 mg daily versus placebo over 5.1 years. [60] The RCT found that lovastatin significantly reduced the incidence of cardiovascular events compared with placebo (6% with lovastatin *v* 21% with placebo; adjusted RR 0.31, 95% CI 0.13 to 0.72; P = 0.03; absolute numbers not reported). However, the RCT found no significant difference between groups in the annualised mean rate of decrease in GFR (–1.3 mL/minute/1.73 m^2/year with lovastatin *v* –1.4 mL/minute/1.73 m^2/year with placebo; P = 0.1), or in the rate of decrease in kidney function loss (defined as decrease in estimated GFR from baseline of 25% or more; adjusted RR 1.10, 95% CI 0.96 to 1.28; P = 0.2). [60]

The fourth subsequent RCT, a subgroup analysis of the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER; 3267 apparently healthy men aged >50 years and women aged >60 years with GFR <60 mL/minute/1.73 m^2, highly sensitive C-reactive protein >2 mg/L, low-density lipoprotein cholesterol <3.3 mmol/L; mean age 70 years; 35% men; mean GFR 56 mL/minute/1.73 m^2; mean proteinuria not reported) compared rosuvastatin 20 mg daily versus placebo over 1.9 years. [61] The RCT found that, compared with placebo, rosuvastatin significantly reduced the risk of the composite outcome of MI, stroke, or cardiovascular death and all-cause mortality (composite outcome: HR 0.59, 95% CI 0.36 to 0.99; P = 0.04; all-cause mortality: HR 0.56, 95% CI 0.37 to 0.85; P = 0.005). However, the RCT found no significant difference between groups for mean GFR levels at 12 months (53.0 mL/minute/1.73 m^2 with rosuvastatin *v* 52.8 mL/minute/1.73 m^2 with placebo; P = 0.44). [61]

Harms: The three systematic reviews did not report any harms. [55] [56] [57]

The first subsequent RCT found similar rates of discontinuation for simvastatin and placebo groups (7% with simvastatin *v* 6% with placebo; P value not reported). [58] Fatal or non-fatal cancer occurred in 60/1143 (5%) people with simvastatin versus 60/1171 (5%) people with placebo (P value not reported). An increase in creatine kinase levels to >10 times the upper limit of normal occurred in 2/1143 (0.2%) people with simvastatin versus 1/1171 (0.1%) people with placebo (P value not reported). Rhabdomyolysis occurred in 1/1143 (0.1%) people with simvastatin and 0/1171 (0%) people with placebo (P value not reported). An increase in aspartate aminotransferase (AST) levels to >3 times the upper limit of normal occurred in 7/1143 (0.6%) people with simvastatin and 11/1171 (0.9%) people with placebo, and an increase in alanine aminotransferase (ALT) occurred in 18/1143 (2%) people with simvastatin and 17/1171 (2%) people with placebo (P value not reported). [58]

The second subsequent RCT gave no information on harms. [59]

The third subsequent RCT reported that only one participant with low GFR experienced a rise in creatine kinase level to >10 times the upper limit of normal, and that patient was in the placebo group. [60] The RCT reported that increases in creatine kinase to >3 times the upper limit of normal were rare (incidence not reported) and the same in both groups (data not reported). [60]

The fourth subsequent RCT reported no statistical or clinically significant difference between rosuvastatin and placebo in the composite outcome of any serious adverse event (P = 0.73); muscular weakness, stiffness, or pain (P = 0.53); myopathy (P = 0.39); rhabdomyolysis (1 with rosuvastatin *v* 0 with placebo; P value not reported); cancer (P = 0.87); gastrointestinal disorders (P = 0.48); renal disorders (P = 0.79); bleeding (P = 0.21); hepatic disorders (P = 0.76); doubling in creatinine level (3 with rosuvastatin *v* 0 with placebo; P value not reported); ALT >3 times the upper limit of normal on consecutive visits (P = 0.41); or haemorrhagic stroke (P = 0.64). [61] However, the RCT found that rosuvastatin significantly increased HbA1c (41 mmol/mol with rosuvastatin *v* 40 mmol/mol with placebo; P = 0.001), but not fasting glucose or physician-reported diabetes compared with placebo (fasting glucose: 5.4 mmol/L with rosuvastatin *v* 5.3 mmol/L with placebo; P = 0.29; physician-reported diabetes: 1.44/100 patient-years with rosuvastatin *v* 1.40/100 patient-years with placebo; P = 0.91). [61]

Comment: Although there is insufficient evidence to recommend the use of statins to prevent decline in renal function, the reviews suggested that it is unlikely that the use of statins for other indications leads to adverse renal effects, and that the cardiovascular benefits seen in other populations extend to people with low glomerular filtration rate (GFR). [55] [56]

OPTION TARGETED LOWERING OF ALBUMINURIA/PROTEINURIA

Disease progression

Compared with non-targeted lowering We don't know if targeted lowering of proteinuria is more effective at reducing the risk of progression to end-stage renal disease (ESRD) in people with chronic renal failure (low-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, **see table, p 25 .**

Benefits:

Targeted versus non-targeted lowering of albuminuria/proteinuria:
We found one RCT (306 people with creatinine 133–442 micromol/L; creatinine clearance 20–70 mL/minute/1.73 m^2; non-diabetic kidney disease and at least 1 g/day proteinuria for at least 3 months; age 49–51 years; mean creatinine 239–256 micromol/L; mean glomerular filtration rate [GFR] 30–31 mL/minute/1.73 m^2; proportion with diabetes not specified; mean 24-hour urine protein excretion 1.4–2.1 g/day) comparing individualised up-titrated benazepril 40 mg daily versus low-dose benazepril 10 mg daily, or individualised up-titrated losartan 200 mg daily versus losartan 50 mg daily with a mean follow-up of 3.7 years. Titration was based on 24-hour urine protein. The RCT is known as Renoprotection of Optimal Antiproteinuric Doses (ROAD). It assessed titrated treatment aimed at lowering 24-hour protein by 10% versus fixed low-dose treatment. [53] See comment.

The titration protocol involved initial doses of benazepril 10 mg daily or losartan 50 mg daily, with 2-weekly assessment of 24-hour urine for proteinuria and weekly assessment of blood pressure, creatinine, and potassium. In the individualised up-titration group, drug doses were up-titrated to the next level (benazepril 10 mg, 20 mg, 30 mg, 40 mg; losartan 50 mg, 100 mg, 150 mg, 200 mg) at 4-week intervals. The dose was down-titrated if the 24-hour urine protein did not fall by 10% or more over the past 4-week period, if hyperkalaemia refractory to medical therapy developed, or if systolic blood pressure decreased to <120 mmHg. People who achieved maximal dose without observing a reduction in 24-hour urine protein of 10% or more resumed initial doses. At the end of up-titration, daily doses in the up-titration benazepril group were 20 mg in 43/84 (51%) people, 30 mg in 11/84 (13%) people, and 40 mg in 6/84 (7%) people; 14/84 (17%) people were off treatment because of intolerance, implying 10/84 (29%) people were on 10 mg; mean daily dose was 20.8 mg. At the end of up-titration, daily doses in the up-titration losartan group were 100 mg in 48/84 (57%) people, 150 mg in 13/84 (15%) people, and 200 mg in 12/84 (14%) people; 6/84 (7%) were off treatment because of intolerance, implying 9/84 (11%) people were on 50 mg; mean daily dose was 118 mg. [53]

The RCT found that up-titrated benazepril significantly reduced the risk of the composite outcome of doubling of serum creatinine, end-stage renal disease (ESRD), or death compared with non-titrated benazepril (15/84 [18%] with up-titrated benazepril *v* 26/83 [31%] with non-titrated benazepril; RR 0.51, 95% CI 0.05 to 0.73; P = 0.02). The RCT found that up-titrated losartan significantly reduced the risk of the composite outcome of doubling of serum creatinine, ESRD, or death compared with non-titrated losartan (13/84 [16%] with up-titrated losartan *v* 26/88 [30%] with non-titrated losartan; RR 0.53, 95% CI 0.05 to 0.74; P = 0.02). [53] The RCT reported similar rates of non-fatal cardiovascular events, MI, heart failure, and stroke in each group (up-titrated benazepril: 5/90 [6%] with non-fatal CVD event, 2/90 [2%] with MI, 1/90 [1%] with heart failure, 1/90 [1%] with stroke; up-titrated losartan: 4/90 [4%] with non-fatal CVD event, 2/90 [2%] with MI, 1/90 [1%] with heart failure, 1/90 [1%] with stroke; non-titrated benazepril: 4/90 [4%] with non-fatal CVD event, 2/90 [2%] with MI, 1/90 [1%] with heart failure, 1/90 [1%] with stroke; non-titrated losartan: 5/90 [6%] with non-fatal CVD event, 2/90 [2%] with MI, 2/90 [2%] with heart failure, 1/90 [1%] with stroke). No significance assessments between groups were reported.

Harms:

Targeted versus non-targeted lowering of albuminuria/proteinuria:
The RCT reported that hyperkalaemia occurred in 3/90 (3%) people with non-titrated benazepril, 5/90 (6%) people with up-titrated benazepril, 3/90 (3%) people with non-titrated losartan, and 5/90 (5%) people with up-titrated losartan; acute decline in renal function occurred in 2/90 (2%) people with non-titrated benazepril, 3/90 (3%) people with up-titrated benazepril, 3/90 (3%) people with non-titrated losartan, and 3/90 (3%) people with up-titrated losartan; dry cough in 17/90 (19%) people with non-titrated benazepril, 15/90 (17%) people with up-titrated benazepril, 0/90 (0%) people with non-titrated losartan, and 0/90 (0%) people with up-titrated losartan; and hypotension in 1/90 (1%) people with non-titrated benazepril, 2/90 (2%) people with up-titrated benazepril, 1/90 (1%) people with non-titrated losartan, and 1/90 (1%) people with up-titrated losartan. [53]

Comment:

Clinical guide:
In this option, we have compared targeted lowering of albuminuria/proteinuria (in which treatments are modified as a result of a person's albuminuria/proteinuria results) versus a non-targeted lowering of albuminuria/proteinuria (in which treatments are given for chronic failure in general but the treatments are modified depending on a range of factors, not specifically a person's albuminuria/proteinuria results).

Proteinuria is associated with progression of renal disease. In RCTs of prevention of progression of renal disease, large reductions in proteinuria were associated with reduced renal disease progression. Therefore, some experts recommend serial measurements of proteinuria or albuminuria

and gradual increases in interventions aimed at reducing proteinuria or progression of it to a specific target (either a proportion reduction, or reduction to less than a defined threshold).

We identified one RCT showing the reduction in doubling of creatinine or ESRD with this approach. However, the comparator doses of ACE inhibitor (benazepril, used at 10 mg/day; the usual dose for hypertension is up to 80 mg/day) and angiotensin II receptor antagonist (losartan, used at 50 mg/day; the usual dose for hypertension is up to 100 mg/day) were low in this study, so that it may also be interpreted as a study of subtherapeutic dose versus therapeutic dose interventions. [53]

OPTION LOWERING BLOOD PRESSURE BELOW USUAL TARGETS

Disease progression
Compared with usual targets We don't know whether lowering blood pressure below usual targets is more effective at reducing glomerular filtration rate (GFR) decline or progression to end-stage renal disease (ESRD) (very low-quality evidence).

Quality of life
Compared with usual targets We don't know whether lowering blood pressure below usual targets is more effective at improving quality of life in people with chronic renal failure (low-quality evidence).

Mortality
Compared with usual targets We don't know whether lowering blood pressure below usual targets is more effective at reducing mortality or combined mortality and morbidity in people with chronic renal failure (very low-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits:

We found no systematic review. We found 6 RCTs (2 of which were reported together in 1 of the publications). [23] [62] [63] [31] [64] [65] The African American Study of Renal Disease (AASK) was reported in 5 publications. [63] [66] [67] [68] [65]

The first RCT (Modification of Diet in Renal Disease [MDRD] study 1, a factorial design trial that also studied a low-protein intervention; see below) studied 585 people with a glomerular filtration rate (GFR) of 25 mL/minute/1.73 m^2 to 55 mL/minute/1.73 m^2 (mean GFR 39 mL/minute/1.73 m^2, standard deviation [SD] 9 mL/minute/1.73 m^2; mean serum creatinine 169 micromol/L, SD 44 micromol/L; mean proteinuria 1.1 g/day, SD 0.2 g/day) assigned to a usual (mean arterial pressure 107 mmHg in people aged at least 60 years, and 113 mmHg in people aged 60 years or less) or low (mean arterial pressure 92 mmHg) blood pressure target. [23] People with various underlying kidney disorders were included (25% with glomerular diseases, 24% with polycystic kidney disease) and a difference in mean arterial pressure between usual and low blood pressure groups of 5 mmHg was achieved. Over 2.2 years' follow-up, end-stage renal disease (ESRD) occurred in 12/585 (2%) people (their distribution between groups was not reported). The projected 3-year mean GFR decline was 1.6 mL/minute lower in the low target blood pressure group compared with the usual target blood pressure group, but the difference was not significant (P = 0.18; absolute numbers not reported).

The second RCT (MDRD study 2) studied 255 people with GFR 13 mL/minute/1.73 m^2 to 24 mL/minute/1.73 m^2 (mean GFR 19 mL/minute/1.73 m^2, SD 3 mL/minute/1.73 m^2; mean serum creatinine 301 micromol/L, SD 80 micromol/L; mean proteinuria 0.9 g/day, SD 0.2 g/day). [23] A difference in mean arterial pressure of 5 mmHg between usual target and low target blood pressure groups was achieved. A total of 94/255 (37%) people reached ESRD (number in each group not reported). There was no significant difference in ESRD between low target blood pressure compared with usual target blood pressure (P = 0.33; 94/255 [37%] people reached ESRD; absolute numbers in each group not reported). Greater proteinuria at baseline in both RCTs was associated with a greater benefit from the low blood pressure target (P = 0.02 for the first RCT; P = 0.01 for the second RCT). [23]

A 10-year follow-up of the people in the two RCTs through national registries of death and ESRD has been reported. [24] Blood pressure control beyond the 2.2 years of the trial was documented 9 months after the end of the study in 491/840 (58%) people, and it showed persistent difference between groups. No subsequent blood pressure measurements were available. In this analysis, low target blood pressure was associated with an improved HR for the development of ESRD and the composite outcome of ESRD or death (ESRD: 268/432 [62%] with low target blood pressure *v* 286/408 [70%] with usual target blood pressure; HR 0.78, 95% CI 0.66 to 0.93; P = 0.0056; composite outcome of ESRD or death: 312/432 [72%] with low target blood pressure *v* 312/408 [76%] with usual target blood pressure; HR 0.85, 95% CI 0.75 to 1.00; P = 0.05). A trend towards greater benefit from low target blood pressure in people with higher baseline proteinuria did not

reach significance in the follow-up data (P = 0.09 for ESRD; P = 0.08 for the composite outcome of ESRD or death; absolute numbers not reported). This study was confounded by differential use of ACE inhibitors (used in 51% of the low target blood pressure group *v* 32% of the usual target group). However, in a sensitivity analysis that adjusted for ACE inhibitor use, the results were similar and the magnitude of the effect was greater than expected for the difference in proportion of people on ACE inhibitors in the two groups. Interpretation of the 10-year follow-up of the first RCT was limited by the paucity of information about participants' blood pressures beyond the end of the trial. In addition, the absence of a protective effect during the trial is difficult to reconcile with the large treatment effect over prolonged follow-up. [24]

In the third RCT (77 people with long-standing hypertension; creatinine >141 micromol/L; protein excretion rate <2 g/day; diastolic blood pressure at least 95 mmHg; all responsive to stepped increases in medication to obtain diastolic blood pressure <80 mmHg during a run-in phase), participants were assigned to low target blood pressure (diastolic blood pressure 65–80 mmHg) or usual target blood pressure (diastolic blood pressure 85–95 mmHg). [62] There were 87 people in the run-in phase, although 10 of these did not reach the target diastolic blood pressure of <80 mmHg and were excluded from the trial. At baseline, GFR was 38 mL/minute/1.73 m^2 (standard error of the mean [SEM] 2 mL/minute/1.73 m^2), serum creatinine was 203 micromol/L (SEM 9 micromol/L), and proteinuria was 0.4 g daily (SEM 0.05 g/day). A difference of 6 mmHg in diastolic blood pressure was achieved between the two groups. At 3.3 years' follow-up, the difference in people with ESRD in the low target blood pressure group compared with the number of people with ESRD in the usual target blood pressure group was not significant (ESRD: 7/35 [20%] people with low blood target pressure *v* 2/42 [5%] with usual target blood pressure; P >0.25). There was no difference between groups in rate of decline of GFR.

The fourth RCT, the AASK, studied 1094 African-Americans with GFR 20 mL/minute/1.73 m^2 to 75 mL/minute/1.73 m^2 (mean GFR about 46 mL/minute/1.73 m^2, SEM 13 mL/minute/1.73 m^2; mean serum creatinine 195 micromol/L, SEM 66 micromol/L in men, 152 micromol/L, SEM 49 micromol/L in women; mean proteinuria 0.6 g/day, SEM 1.0 g/day in men, 0.4 g/day, SEM 0.6 g/day in women) with no identified cause for renal disease other than hypertension. [63] This open-label RCT used a 2 × 3 factorial design in which participants were randomised to low target blood pressure (mean arterial pressure 92 mmHg) or usual target blood pressure (mean arterial pressure 102–107 mmHg) and one of three medications: ramipril, metoprolol, or amlodipine. A 10-mmHg difference between groups was achieved and maintained throughout most of the study. Over the 4-year follow-up period, the rate of GFR decline did not differ between the low target blood pressure group and the usual target blood pressure group (GFR slope from baseline –2.21 mL/minute/1.73 m^2 a year with low target blood pressure *v* –1.95 mL/minute/1.73 m^2 a year with usual target blood pressure; P = 0.24). The composite outcome (decrease in GFR by 50%, decrease in GFR by at least 25 mL/minute/1.73 m^2, ESRD, or death) did not significantly differ between the groups (8.1% a year with low target blood pressure group *v* 7.6% a year with usual target blood pressure; P = 0.85). The RCT found no significant differences in results (assessed as effect on change in GFR; results not reported) when stratified by baseline proteinuria.

The fourth RCT found no significant difference between usual and low target blood pressure in cardiovascular mortality (included death from stroke, congestive heart failure, or coronary artery disease), composite outcome of cardiovascular mortality or admission to hospital for CVD, ESRD, or all cardiovascular events, including multiple events in the same person (cardiovascular mortality: HR 0.98, 95% CI 0.48 to 2.01; P = 0.96; composite outcome of cardiovascular mortality or admission to hospital for CVD: HR 0.84, 95% CI 0.61 to 1.16; P = 0.29; ESRD: HR 0.91, 95% CI 0.72 to 1.15; P = 0.42; all cardiovascular events: HR 1.06, 95% CI 0.76 to 1.49; P = 0.73; absolute numbers not reported). [66]

The fourth RCT found no significant difference in mean change in composite physical health or the composite mental health outcomes of the Short Form 36 between groups over the 4 years of the study (reported as not significant; data presented graphically; P value not reported). [67]

A pilot study for the fourth RCT examined quality of life in 84 people assigned to low and usual target blood pressure groups, using Short Form 36. The duration of the trial was not specified. Scores were similar at the start of the study, but, by the end of the study, low target blood pressure significantly decreased scores for vitality and general health compared with usual target blood pressure (vitality measured on a quality of life and symptom score, range 0–100: 52.7 with low target blood pressure *v* 65.1 with usual target blood pressure; P <0.001; general health measured on a quality of life and symptom score, range 0–100: 55.1 with low target blood pressure *v* 64.3 with usual target blood pressure; P = 0.018). [68]

Long-term follow-up of the fourth RCT found no significant difference between intensive control and standard control of blood pressure in the combined outcome of progression of chronic kidney

disease (defined as doubling of serum creatinine levels), diagnosis of ESRD, or death after total follow-up of 8.8 to 12.2 years (282/540 [7.3% a year] with intensive control *v* 285/554 [7.5% a year] with standard control; HR 0.91, 95% CI 0.77 to 1.08; P = 0.27). [65] The study also found no significant difference between groups in doubling of creatinine or ESRD (doubling of creatinine: 213/540 [5.5% a year] with intensive control *v* 209/554 [5.5% a year] with standard control; HR 0.95, 95% CI 0.78 to 1.5; P = 0.59; ESRD: 238/540 [5.8% a year] with intensive control *v* 256/554 [6.3% a year] with standard control; HR 0.85, 95% CI 0.71 to 1.02; P = 0.08). However, subgroup analysis of people with baseline urine protein-to-creatinine ratio >0.22 found that intensive control significantly reduced the combined outcome of progression of chronic kidney disease (defined as doubling of serum creatinine levels), diagnosis of ESRD, or death (136/181 [14% a year] with intensive control *v* 149/176 [19% a year] with standard control, HR 0.73, 95% CI 0.58 to 0.93; P = 0.01); doubling of creatinine or ESRD (114/181 [12% a year] with intensive control *v* 126/176 [16% a year]) with standard control, HR 0.76, 95% CI 0.58 to 0.99; P = 0.04); and ESRD or death (118/181 [11% a year] with intensive control *v* 143/176 [16% a year] with standard control, HR 0.67, 95% CI 0.52 to 0.87; P = 0.002). [65]

In the fifth RCT (Second Ramipril Efficacy in Nephropathy trial [REIN 2]; 338 people who had creatinine clearance <45 mL/minute/1.73 m^2 and proteinuria 1–3 g/day, or creatinine clearance <70 mL/minute/1.73 m^2 and proteinuria >3 g/day), people were randomised to low target blood pressure (systolic blood pressure <130 mmHg and diastolic blood pressure <85 mmHg) or usual target blood pressure (diastolic blood pressure <90 mmHg). [31] At baseline, mean GFR was 34 mL/minute/1.73 m^2 (SD 18 mL/minute/1.73 m^2), mean creatinine was 238 micromol/L (SD 97 micromol/L), and proteinuria was 2.9 g daily (SD 1.9 g/day). All people were treated with ramipril (84% on 5 mg/day, 16% on 2.5 mg/day). Felodipine was used as the first additional agent in the low target blood pressure group. A difference between groups of about 4 mmHg in systolic blood pressure and 3 mmHg in diastolic blood pressure was maintained throughout the study. Over the 1.4 years' follow-up, low target blood pressure did not decrease progression to ESRD compared with usual blood pressure (38/167 [23%] with low target blood pressure *v* 34/168 [20%] with usual target blood pressure; adjusted for prespecified baseline covariates; HR 1.00, 95% CI 0.61 to 1.64; P = 0.99). In people with baseline proteinuria 3 g daily or greater, the adjusted HR was 1.09 (95% CI 0.55 to 2.19; P = 0.81), and in people with baseline proteinuria of 1–3 g daily, the adjusted HR was 1.06 (95% CI 0.51 to 2.20; P = 0.89). The trial was terminated early on the advice of its safety monitoring committee.

The sixth open-label RCT (128 people with a clinical diagnosis of idiopathic chronic glomerulonephritis and urine protein-creatinine ratio of >1 g/g confirmed on 2 occasions; mean age 53 years; 64% men; 63% undiagnosed chronic kidney disease; 16% focal and segmental glomerulosclerosis; 22% IgA nephropathy; mean baseline estimated GFR [eGFR] 63.5 mL/minute/1.73 m^2; mean urine protein-creatinine ratio 2.6 g/g, mean baseline blood pressure 156/93 mmHg) compared intensive blood pressure lowering (and intensive renin-angiotensin system blockade) therapy (ramipril 10 mg/day plus irbesartan 300 mg/day plus spironolactone 25 mg/day plus atorvastatin 20 mg/day) versus standard therapy (ramipril 10 mg/day plus atorvastatin 10 mg/day) over 36 months. [64] The RCT found that, compared with standard therapy, intensive therapy significantly lowered systolic blood pressure (decreasing from 157 mmHg to 114 mmHg with intensive therapy *v* from 156 mmHg to 122 mmHg with standard therapy; P <0.01) and significantly improved rate of decrease of eGFR (changing from 65 mL/minute/1.73 m^2 to 63 mL/minute/1.73 m^2 with intensive therapy *v* changing from 63 mL/minute/1.73 m^2 to 56 mL/minute/1.73 m^2 with standard therapy; P <0.01). [64]

Harms:

In the first RCT (MDRD study 1), significantly more people reported "feeling faint" in the low target blood pressure group compared with the usual target blood pressure group (15% of follow-up visits/person in the low blood pressure group *v* 12% of follow-up visits/person in the usual blood pressure group; P = 0.012). [23]

In the second RCT (MDRD study 2), there was no significant difference between low and usual target blood pressure groups in people who reported "feeling faint" (18% of follow-up visits/person in the low blood pressure group *v* 12% of follow-up visits/person in the usual blood pressure group; P = 0.009). Significantly more people in the low target blood pressure group had persistent symptoms of hypotension requiring a reduction in antihypertensive medication (3.2% in the low blood pressure group *v* 0.7% in the usual blood pressure group; P = 0.01). [69]

The third RCT did not report any harms. [62]

The fourth RCT reported no significant difference between low and usual target blood pressure groups after 4 years in cardiovascular death, cardiovascular events, hyperkalaemia, angio-oedema, shortness of breath, syncope, dizziness, oedema, or sexual dysfunction (cardiovascular death: 0.6% with low target blood pressure *v* 0.7% with usual target blood pressure; cardiovascular events: 2.3% with low target blood pressure *v* 2.7% with usual target blood pressure; hyperkalaemia: 0%

with low target blood pressure *v* 0.7% with usual target blood pressure; angio-oedema: 3.5% with low target blood pressure *v* 5.4% with usual target blood pressure; shortness of breath: 57% with low target blood pressure *v* 46% with usual target blood pressure; syncope: 6% with low target blood pressure *v* 5% with usual target blood pressure; dizziness: 53% with low target blood pressure *v* 49% with usual target blood pressure; oedema: 55% with low target blood pressure *v* 54% with usual target blood pressure; sexual dysfunction: 30% with low target blood pressure *v* 27% with usual target blood pressure; P >0.05; absolute numbers not reported). [63] However, cough occurred in more people in the low compared with the usual target blood pressure group (55% with low target blood pressure *v* 47% with usual target blood pressure; P <0.05; absolute numbers not reported). [63]

The pilot study of quality of life [68] and the long-term cohort follow-up of the ASSK trial did not report on harms. [65]

In the fifth RCT, 2/167 (1%) people died in the low target blood pressure group compared with 3/168 (2%) people in the usual target blood pressure target group (significance assessment not reported). [31] More serious adverse effects were reported in the low target blood pressure group compared with the usual target blood pressure group (37/167 [22%] with low target blood pressure *v* 25/168 [15%] with usual target blood pressure; significance assessment not reported). There was no severe hyperkalaemia in either group.

The sixth RCT reported that 13% of people in the standard therapy group and 23% in the intensive therapy group withdrew from the study because of adverse effects such as hyperkalaemia, cough, estimated GFR decrease of >30% from baseline, and hypotension (hyperkalaemia: potassium >5.5 mmol/L; 3/64 [2%] with standard therapy *v* 9/64 [6%] with intensive therapy; cough: 2/64 [0.3%] with standard therapy *v* 1/64 [1.7%] with intensive therapy; estimated GFR decrease of >30% from baseline: 1/64 [1%] with standard therapy *v* 0/64 [0%] with intensive therapy; hypotension (0/64 [0%] with standard therapy *v* 3/64 [2%] with intensive therapy). The RCT reported that 9/64 (6%) people in the intensive arm developed gynaecomastia but none stopped the intervention because of this. It also reported that 12/64 (8%) people on standard therapy and 31/64 (20%) on intensive therapy had to interrupt study intervention for <10 days because of low blood pressure that occurred at the same time as episodes of diarrhoea, dehydration, or fever. [64]

Comment: None.

OPTION ERYTHROPOIESIS-STIMULATING AGENTS New

Mortality
Compared with placebo or lower haemoglobin targets Erythropoiesis-stimulating agents or higher haemoglobin targets do not seem to be more effective at reducing mortality in people with anaemia and chronic kidney disease (moderate-quality evidence).

Disease progression
Compared with placebo or lower haemoglobin targets Erythropoiesis-stimulating agents or higher haemoglobin targets do not seem to be more effective at reducing the rate of progression to end-stage renal disease (ESRD) in people with anaemia and chronic kidney disease (moderate-quality evidence).

Cardiovascular effects
Compared with placebo or lower haemoglobin targets Erythropoiesis-stimulating agents or higher haemoglobin targets increase the risk of stroke, and do not seem more effective at reducing other serious cardiovascular events in people with anaemia and chronic kidney disease (moderate-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits: We identified two systematic reviews. [70] [71] The first review [70] included 13 of 14 studies included in the second review. [71] The second systematic review included single arm and parallel group studies and did not report quantitative synthesis of data; therefore, only the first review is reported here.

The first review (search date 2009, 27 RCTs, 10,452 people with anaemia and chronic kidney disease) compared erythropoiesis-stimulating agents (ESAs) versus placebo or different doses of ESAs for higher versus lower targets of haemoglobin. [70] Trials of people with end-stage renal disease (ESRD) and people with diabetes of at least 3 months' duration were included. [70]

The review found that ESAs or higher haemoglobin targets using ESAs significantly increased rates of stroke compared with placebo or lower haemoglobin targets (6 RCTs; 127/3529 [4%] with ESAs or higher haemoglobin targets *v* 77/3525 [2%] with placebo or lower haemoglobin targets;

RR 1.51, 95% CI 1.03 to 2.21). [70] The review found no significant differences between groups in the risk of mortality, serious cardiovascular events, or end-stage kidney disease (mortality: 18 RCTs; 731/4951 [15%] with ESAs or higher haemoglobin targets *v* 677/5000 [14%] with placebo or lower haemoglobin targets; RR 1.09, 95% CI 0.99 to 1.20; serious cardiovascular events: 7 RCTs; 878/3438 [26%] with ESAs or higher haemoglobin targets *v* 800/3442 [23%] with placebo or lower haemoglobin targets; RR 1.15, 95% CI 0.98 to 1.33; end-stage kidney disease: 10 RCTs; 704/3619 [19%] with ESAs or higher haemoglobin targets *v* 687/3699 [18%] with placebo or lower haemoglobin targets; RR 1.08, 95% CI 0.97 to 1.20). [70] The review reported that the evidence for treatment effects on quality of life was low quality, with high risk for bias due to selective reporting of outcomes; therefore, no quantitative analysis was attempted. However, the review noted that the large well-designed Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) trial [72] observed no difference in Short Form-36 scores between groups in energy or physical function quality-of-life domains (see comment). [70]

Harms: The first systematic review found that ESAs or higher haemoglobin targets using ESAs were associated with increased risk for stroke (RR 1.51, 95% CI 1.03 to 2.21). [70]

Comment: The results of the first systematic review were dominated by the results of the placebo-controlled TREAT trial, [72] performed in people with low glomerular filtration rate (GFR) who also had type 2 diabetes at entry. These people were selected because they have a higher event rate than people without diabetes, which rendered the trial feasible, rather than because of any prespecified hypothesis that people with diabetes would have a response to ESAs different from that of people without diabetes. Therefore, it is likely that these results are generalisable to a non-diabetic population with chronic kidney disease.

Clinical guide:
The TREAT trial found that use of darbepoetin (an ESA) was associated with fewer transfusions compared with placebo, although many people in the darbepoetin group were transfused (297/2012 [15%] with darbepoetin *v* 496/2026 [24%] with placebo; P <0.001). [72] The minimisation of transfusion is particularly of benefit in people with progressive renal disease who are likely to reach ESRD when they are still of an age where transplantation is an option (varies between countries, but often 70 years or younger in developed countries with access to transplantation): blood transfusion is sensitising (meaning that it leads to the development of anti-HLA antibodies), and sensitisation leads to difficulties in finding a suitable transplant donor for a previously transfused patient at or nearing ESRD. However, haemoglobin <100 g/L occurs in only about 20% of people with GFR <30 mL/minute (in clinical practice, usually in patients with progressive disease and GFR <20 mL/minute), and is uncommon in patients with GFR 30 mL/minute to 60 mL/minute (and likely to be unrelated to the renal disease). [73] Patients with GFR <30 mL/minute and haemoglobin <100 g/L should probably be managed in conjunction with a nephrologist, where one is available. This would facilitate optimal assessment of the risks and benefits of the use of an ESA and incorporation of the patient's individual clinical circumstances and preferences. Most of the data on the increased risk of stroke comes from a study in which the haemoglobin target was near normal. [74] It is possible that benefits can be realised and risks minimised by targeting a haemoglobin level closer to that observed in the placebo group in this study, around 95 g/L to 100 g/L. Any benefit in terms of prevention of transfusion will be less with a lower target. The possibility of improving quality of life with ESAs by targeting haemoglobin of 95 g/L to 100 g/L, in the small proportion of patients whose haemoglobin falls below that threshold without an alternative cause, is derived by generalisation from a small early randomised trial in people on haemodialysis comparing a true placebo group (haemoglobin 74 g/L) with an ESA treated group (haemoglobin 102 g/L). [74]

QUESTION What are the effects of lifestyle changes used to reduce progression rate of chronic renal failure?

OPTION PSYCHOEDUCATIONAL INTERVENTIONS

Disease progression
Compared with standard procedures or control Educational interventions including enhanced education programmes may be more effective than standard education programmes or control at reducing the time to requirement of renal replacement therapy, and at reducing the number of people who start dialysis or who have renal transplantation (low-quality evidence).

Mortality
Compared with usual care We don't know whether educational interventions are more effective at reducing mortality (very low-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits: We found three RCTs. [75] [76] [77]

The first RCT (204 people, mean age 50.2 years; serum creatinine >350 micromol/L) compared standard education procedures versus an enhanced education programme. [75] Standard education procedures varied between centres. The enhanced education programme consisted of a 75-minute slide presentation by a research assistant, and the slide contents were given in a booklet to the participants. The time to requirement of renal replacement therapy was 4.6 months longer for people in the enhanced education programme group compared with those in the standard education group (P <0.05).

The second RCT randomised 297 people with chronic kidney disease (mean age 58.6 years; 60.3% men; 38–44% with diabetes; mean serum creatinine levels 419 micromol/L; mean glomerular filtration rate [GFR] and mean proteinuria not reported) to a 90-minute intervention conducted by social workers (who received training in a 2-day workshop) or to usual care, which differed between centres and included education in many cases. [76] The intervention was a personalised one-to-one slide-illustrated presentation covering healthy kidney function, kidney diseases, haemodialysis, continuous ambulatory peritoneal dialysis, renal transplantation, dietary and drug treatment regimens, nutrition, and lifestyles. The content was summarised in a 60-page booklet that participants in the intervention arm received for future reference. During the first 18 months of follow-up, the social worker called the person every 3 weeks for a maximum of 10 minutes to review illness-related developments in each of 13 life domains relevant to quality of life in renal disease. During the course of this conversation, the social workers encouraged the participants to inform their nephrologists and seek help for any problems that might merit professional attention. Social workers were instructed not to intervene directly or attempt a psychotherapeutic intervention. At 18 months' follow-up, educational intervention reduced the number of people who started dialysis or had renal transplantation compared with control; however, more people in the educational intervention group than in the control group died before starting dialysis (started dialysis: 89/149 [60%] with educational intervention *v* 106/148 [72%] with control; P <0.001; had renal transplantation as their first renal replacement therapy: 3/149 [2%] with educational intervention *v* 7/148 [5%] with control; significance not reported; died before starting dialysis: 19/149 [13%] with educational intervention *v* 11/148 [7%] with control; significance not reported). The median time to renal replacement therapy was significantly less with educational intervention compared with controls (14 months with educational intervention *v* 17 months with control; P <0.001).

The third RCT (355 people with a serum creatinine of 350 micromol/L and increasing, or for whom renal replacement therapy was imminently required; mean age 47.4 years, standard deviation [SD] 15.4 years; 58% employed; 29% post-secondary education; mean GFR, mean serum creatinine, and mean proteinuria not reported) randomised people to a pre-dialysis psychoeducational intervention (172 people) or to usual care (163 people). [77] The intervention entailed a single one-to-one slide lecture presentation that provided information about: normal functions of the kidneys; diseases of the kidneys; dietary management of renal disease; and alternative modes of renal replacement therapy, including maintenance haemodialysis, peritoneal dialysis, and renal transplantation. Drug regimens and dietary and fluid intake restrictions received limited coverage. Participants were given ample opportunity to ask questions, and received a 22-page booklet summarising the content for future reference. A health educator (educated to Bachelor's degree level) was trained specifically to deliver the pre-dialysis psychoeducational intervention in a consistent and standard fashion. The pre-dialysis psychoeducational intervention session required 60 to 75 minutes to complete. At 8.5 years' follow-up (SD 7.23 years; adjusted for age, general non-renal health at inception, and time between identification and pre-dialysis psychoeducational intervention or usual care), people in the psychoeducational intervention group survived longer compared with people in the usual care group (median survival: 7.84 years with psychoeducational intervention *v* 5.07 years with usual care; HR 1.32, 95% CI 1.00 to 1.74; P = 0.053; median survival after the initiation of dialysis therapy: 4.57 years with psychoeducational intervention *v* 3.91 years with usual care, HR 1.35, 95% CI 1.02 to 1.78; P = 0.036).

Harms: The RCTs did not report any harms. [75] [76] [77]

Comment: Cognitive and sensory impairments will limit the applicability of these results for all people. This is particularly relevant given the advanced age of many people new to dialysis.

OPTION SODIUM (DIETARY)

We found no direct information from RCTs about effects of dietary sodium in people with chronic renal failure.

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits: We found no systematic review or RCTs assessing the effects of dietary sodium on chronic renal failure.

Harms: We found no RCTs.

Comment: None.

OPTION EXERCISE

Disease progression
Compared with no exercise We don't know whether exercising up to 30 minutes a day is more effective at reducing glomerular filtration rate (GFR) or end-stage renal disease (ESRD) in people with chronic renal failure (low-quality evidence).

Mortality
Compared with no exercise We don't know whether exercising up to 30 minutes a day is more effective at reducing mortality in people with chronic renal failure (low-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits: We found no systematic review. We found one RCT comparing an exercise programme designed to match each person's physical capacity versus no exercise (30 people, aged 22–70 years; mean maximal oxygen capacity 25 mL/minute/kg; mean glomerular filtration rate (GFR) 26 mL/minute/1.73 m^2; mean serum creatinine and mean proteinuria not reported). [78] The intervention (15 people) consisted of bicycle ergometer exercise at home, running, swimming, and walking, gradually increased in duration (up to about 30 minutes/day) and intensity (up to 60–75% of maximal exercise capacity based on monthly calibration of heart rate against maximal oxygen consumption). Controls (15 people) received no exercise. At a minimum of 1.5 years' follow-up, end-stage renal disease (ESRD), mortality, and GFR were similar in the exercise and control groups (ESRD: 3/15 [20%] with exercise *v* 2/15 [13%] with control; mortality: 0/15 [0%] with exercise *v* 1/15 [7%] with control; significance not reported; median change in GFR by plasma ^{51}Cr ethylenediaminetetra-acetic acid [EDTA] clearance: –0.27 mL/minute/1.73 m^2/month with exercise *v* –0.28 mL/minute/1.73 m^2/month; reported as not significant; P value not reported for any outcome).

Harms: The RCT did not report any harms. [78]

Comment: The benefits of exercise in people with chronic renal failure are likely to be cardiovascular rather than renal. However, the RCT provided limited evidence that exercise does not lead to more rapid decline in GFR.

OPTION SMOKING CESSATION

We found no direct information from RCTs about the effects of smoking cessation in people with chronic renal failure.

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits: We found no systematic review or RCTs assessing the effect of smoking cessation in chronic renal failure.

Harms: We found no RCTs.

Comment: None.

OPTION STRUCTURED PROGRAMMES TO ACHIEVE THERAPEUTIC GOALS

Disease progression
Compared with usual care Structured programmes (involving a multidisciplinary team to achieve therapeutic goals) and usual care seem equally effective at reducing serum creatinine levels in people with chronic renal failure (moderate-quality evidence).

Mortality
Compared with usual care Structured programmes (involving a multidisciplinary team to achieve therapeutic goals) and usual care seem equally effective at reducing cumulative mortality in people with chronic renal failure (moderate-quality evidence).

For GRADE evaluation of interventions for chronic renal failure, see table, p 25 .

Benefits: We found one RCT, which randomised 437 people (mean age 68–69 years, standard deviation [SD] 11 years; mean serum creatinine 186 micromol/L; calculated Cockcroft-Gault creatinine clearance 34 mL/minute, SD 10 mL/minute; proteinuria not reported) attending two of 4 general medicine practices to an intervention consisting of visits to a nephrology case management clinic for evaluation, and treatment by a nephrologist or nephrology fellow, a renal nurse, a renal dietician, and a social worker at regular intervals (between 3 and 6 months) determined by the enrolment serum creatinine level. [79] The programme included avoidance of nephrotoxins, use of ACE inhibitors, improving blood pressure control, decreasing protein intake, and decreasing barriers to care. Communication was maintained with the primary care physician. Additional visits with a nephrologist were scheduled as needed. When people were admitted to hospital for any reason, the team reviewed the inpatient care and provided suggestions where relevant. People attending control practices received usual care, including referral to nephrologists at the discretion of the primary care team. After 3 to 5 years' follow-up, the specialist structured programme did not significantly reduce serum creatinine, admissions to hospital, or mortality compared with receiving usual primary care (creatinine clearance: 30 mL/minute, SD 16 mL/minute with specialist structured programme *v* 34 mL/minute, SD 23 mL/minute with usual primary care; P = 0.10; admissions to hospital: 1.3 mL/minute, SD 1.8 mL/minute with specialist structured programme *v* 1.3 mL/minute, SD 2.1 mL/minute with usual primary care; P = 0.94; cumulative mortality: 59/206 [29%] with specialist structured programme *v* 77/230 [33%] with usual primary care; P = 0.29).

Harms: The RCT did not report any harms. [79]

Comment: Numerous cohort studies have shown reduced morbidity and mortality when people are referred to nephrologists <3 months before they need to start dialysis. Given the importance of educational interventions (see option psychoeducational interventions, p 17) and the importance of physical preparation for renal replacement therapy (access creation for either haemodialysis or peritoneal dialysis; transplant assessment of donor and recipient for pre-emptive live related transplantation), there is little doubt that people should be referred to nephrologists many months before they require renal replacement therapy, perhaps when glomerular filtration rate (GFR) is about 20 mL/minute. Although many disciplines will be involved in the care of such people, direct evidence for the importance of a formal multidisciplinary team or programme is lacking. Whether people with higher GFRs benefit from nephrological care or multidisciplinary nephrological care is not known.

Structured programmes were defined as those that routinely used a multidisciplinary intervention involving at least one other team member (e.g., nursing, dietary, diabetic management, social work) in addition to care by a physician.

GLOSSARY

Chronic renal insufficiency Chronic renal failure.

Creatinine clearance A method of estimating kidney function (glomerular filtration rate) by either direct measurement of creatinine concentration in blood and a timed urine collection, or by estimation from age, weight, sex, and serum creatinine using an empiric equation.

Proteinuria The excretion of protein in the urine, usually described as pathological when in excess of 0.3 g/day.

Renal replacement therapy Dialysis or renal transplantation.

Chronic kidney disease Defined by the Kidney Disease Improving Global Outcomes (KDIGO) statement as either the presence of abnormalities in urine or imaging that may lead to progressive disease or creatinine clearance (or glomerular filtration rate) <60 mL/minute/1.73 m^2. Chronic kidney disease includes chronic renal failure, but it also includes predictors of chronic renal failure in people with normal kidney function (e.g., proteinuria) and end-stage renal disease (ESRD).

Chronic renal failure Chronically (at least 3 months' duration) reduced kidney function (clearance, glomerular filtration rate [GFR]). Renal function declines normally with age, and the exact level of decline at a given age that should be considered pathological is not known. The Kidney Disease Improving Global Outcomes (KDIGO) statement considers a GFR of <60 mL/minute1.73 m^2 pathological at all ages. However, many older people have values less than this (in the US, about 7% of white people without diabetes who are aged in their 60s and 15% of those aged in their 70s), and the extent to which low kidney function in the range of 30 mL/minute/1.73 m^2 to 60 mL/minute/1.73 m^2 is pathological or progressive in all people is a subject of some controversy. Although people with end-stage renal disease (ESRD), by definition, have chronic failure of their kidneys (which may have resulted from an acute or a chronic process), they are generally not included in the term chronic renal failure, which in most of the literature and in this review refers exclusively to those with low kidney function who are not treated with renal replacement therapy.

End-stage renal disease (ESRD) Irreversible decline in a person's own kidney function, which is treated with renal replacement therapy in the form of dialysis or renal transplantation.

Glomerular filtration rate (GFR) The rate of elaboration of protein-free plasma filtrate (ultrafiltration) across the walls of the glomerular capillaries. GFR is used as a measure of the clearance, or capacity to remove toxins, of the

kidney. Although the kidneys have many different functions, it is specifically clearance that is referred to as "renal function" or "kidney function". GFR can be measured by inulin clearance (the criterion measure), by urine or plasma clearance of radioactive or contrast materials, estimated from the creatinine clearance calculated from a timed urine specimen, or from the mean or creatinine and urea clearances from a timed urine specimen, or calculated from serum creatinine and clinical data as either an estimated GFR or estimated creatinine clearance.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Short Form Health Survey (SF-36) is a 36-item scale measuring general health, mental health, physical function, social functioning, bodily pain, and role limitation owing to physical health problems or emotional health problems. Standardised scores range from 0 to 100.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Erythropoiesis-stimulating agents New option added with two systematic reviews. [70] [71] Categorised as Likely to be ineffective or harmful.

Lowering blood pressure below usual targets New evidence added. [64] [65] Categorisation unchanged (Unlikely to be beneficial).

Statins New evidence added. [57] [60] [61] Categorisation unchanged (Unknown effectiveness), as there remains insufficient evidence on the effects of statins on the progression of renal failure.

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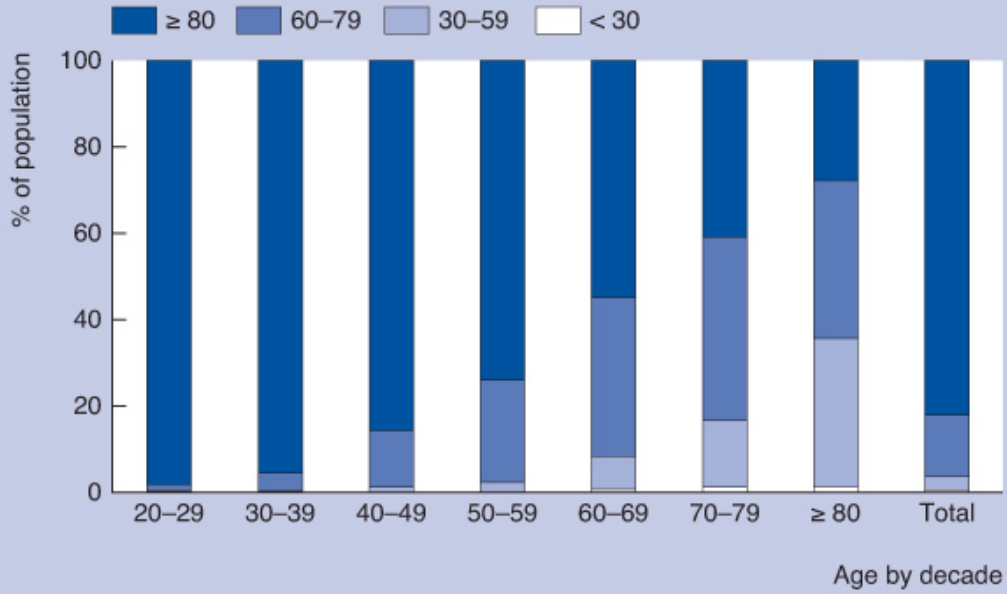
Competing interests: CC has worked as a consultant for Bayer. CC is the author of several papers referenced in this review.



Weighted distribution of predicted glomerular filtration rate by the modification of diet in renal diseases equation, by age (in decades), for adults without diabetes in third national health and nutrition examination survey. Estimates are calculated after subtraction of 20.3 µmol/L from serum creatinine concentration to account for differences between White Sands and Cleveland clinic laboratories. Values are given in mL/min/1.73 m^2. Modified from Clase et al[9]

FIGURE 1 **Prevalence of low glomerular filtration rate (GFR) in the US general population.**

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TABLE 1 **Rate of change of glomerular filtration rate (GFR) in non-referred people with elevated creatinine.** [5]

		Rate of decline in GFR (mL/minute/1.73 m^2/year)				
Age (years)	**Sex**	**<2.0**	**2.0–2.9**	**3.0–3.9**	**4.0–4.9**	**5.0 or more**
<70	Men (%)	81.7	2.4	4.8	4.8	6.3
	Women (%)	82.4	4.4	4.4	4.4	4.4
	All (%)	82.0	3.6	4.6	4.6	5.2
70–80	Men (%)	79.8	4.1	3.8	4.1	8.2
	Women (%)	82.9	5.1	3.8	2.4	5.8
	All (%)	81.7	4.7	3.7	3.1	6.8
80+	Men (%)	76.7	4.8	2.9	4.2	11.5
	Women (%)	77.6	5.8	3.9	3.9	8.8
	All (%)	77.3	5.5	3.4	4.0	9.8
All	Men (%)	78.5	4.3	3.3	4.3	9.6
	Women (%)	79.6	5.5	3.9	3.5	7.5
	All (%)	79.3	5.0	3.7	3.7	8.3

GFR, glomerular filtration rate, calculated using the Modification of Diet in Renal Disease (MDRD) formula.

TABLE GRADE evaluation of interventions for chronic renal failure

Important outcomes	Renal disease progression, cardiovascular effects, quality of life, mortality, and adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of drug treatments used to reduce progression rate of chronic renal failure?									
12 (2084) [36] [22]	Disease progression	ACE inhibitors *v* control	4	–1	0	–1	0	Low	Quality point deducted for no ITT analysis in 1 RCT. Directness point deducted for composite outcome in 1 RCT
12 (10,364) [36] [22] [37]	Mortality	ACE inhibitors *v* control	4	–1	–1	–1	0	Very low	Quality point deducted for no ITT analysis in 1 RCT. Consistency point deducted for conflicting results. Directness point deducted for composite outcome in 1 RCT
4 (453) [22] [38] [39] [41]	Disease progression	ACE inhibitors plus angiotensin II receptor antagonists *v* ACE inhibitors/angiotensin II receptor antagonists alone	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for differences in disease severity included affecting generalisability of results
1 (1046) [46]	Disease progression	Fibrates *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and subgroup analysis of larger study
2 (165) [50] [51]	Disease progression	Angiotensin II receptor antagonists *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and no ITT analysis
2 (374) [52] [53]	Disease progression	Angiotensin II receptor antagonists *v* ACE inhibitors	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of data. Consistency point deducted for conflicting results. Directness point deducted for composite outcome in 1 RCT
1 (33) [54]	Disease progression	Nicotinates *v* no nicotinates	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for lack of data on long-term clinical outcomes
30 (53,631) [55] [57] [59] [60] [61]	Disease progression	Statins *v* placebo or no treatment	4	0	–2	0	0	Low	Consistency points deducted for heterogeneity among RCTs and for different results in 2 meta-analyses including many of the same trials
28 (30,598) [56] [58] [61]	Mortality	Statins *v* placebo or no treatment	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of data
3 (5885) [58] [60] [61]	Cardiovascular effects	Statins *v* placebo or no treatment	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of data. Directness point deducted for the use of combined outcome
1 (306) [53]	Disease progression	Targeted lowering *v* non-targeted lowering of albuminuria/proteinuria	4	0	0	–2	0	Low	Directness points deducted for use of subtherapeutic doses in control group and use of composite outcomes
6 (2477) [23] [31] [62] [63] [64] [65]	Disease progression	Lowering blood pressure below usual targets *v* usual targets	4	–2	0	–2	0	Very low	Quality points deducted for incomplete reporting of results and inclusion of open-label RCT. Directness points deducted for range of disease severity included and for composite outcome

Important outcomes	Renal disease progression, cardiovascular effects, quality of life, mortality, and adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (1094) [67] [68]	Quality of life	Lowering blood pressure below usual targets *v* usual targets	4	–2	0	–1	0	Low	Quality points deducted for incomplete reporting of results and inclusion of open-label RCT. Directness point deducted for composite outcome
4 (3028) [23] [63] [66]	Mortality	Lowering blood pressure below usual targets *v* usual targets	4	–2	–1	–2	0	Very low	Quality points deducted for incomplete reporting of results and inclusion of open-label RCT. Consistency point deducted for conflicting results (sub-analysis of 2 RCTs). Directness points deducted for range of disease severity included and for composite outcome
18 (9951) [70]	Mortality	Erythropoiesis-stimulating agents or higher haemoglobin target *v* placebo or lower haemoglobin target	4	0	0	–1	0	Moderate	Directness point deducted for the use of combined intervention reporting
10 (7318) [70]	Disease progression	Erythropoiesis-stimulating agents or higher haemoglobin target *v* placebo or lower haemoglobin target	4	0	0	–1	0	Moderate	Directness point deducted for the use of combined intervention reporting
7 (at least 7054) [70]	Cardiovascular effects	Erythropoiesis-stimulating agents or higher haemoglobin target *v* placebo or lower haemoglobin target	4	0	0	–1	0	Moderate	Directness point deducted for the use of combined intervention reporting
What are the effects of lifestyle changes used to reduce progression rate of chronic renal failure?									
2 (501) [75] [76]	Disease progression	Educational interventions *v* standard procedures/control	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for applicability of findings
2 (652) [76] [77]	Mortality	Standard education *v* enhanced education programmes	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for applicability of findings
1 (30) [78]	Disease progression	Exercise *v* no exercise	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (30) [78]	Mortality	Exercise *v* no exercise	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (437) [79]	Disease progression	Structured programmes to achieve therapeutic goals *v* usual care	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about benefit
1 (437) [79]	Mortality	Structured programmes to achieve therapeutic goals *v* usual care	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about benefit

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. ITT, intention to treat. Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.